Pesticides and Childhood Cancers

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To evaluate the possible association between pesticides and the risk of childhood cancers, epidemiologic studies published between 1970 and 1996 were critically reviewed. Thirty-one studies investigated whether occupational or residential exposure to pesticides by either parents or children was related to increased risk of childhood cancer. In general, the reported relative risk estimates were modest. Risk estimates appeared to be stronger when pesticide exposure was measured in more detail. Frequent occupational exposure to pesticides or home pesticide use was more strongly associated with both childhood leukemia and brain cancer than either professional exterminations or the use of garden pesticides. Occupational pesticide exposure was also associated with increased risk of Wilms' tumor, Ewing's sarcoma, and germ cell tumors. Residence on a farm, a proxy for pesticide exposure, was associated with increased risk of a number of childhood cancers. Although increased risk of some childhood cancers in association with pesticide exposure is suggested by multiple studies, methodological limitations common to many studies restrict conclusions; these include indirect exposure classification, small sample size, and potential biases in control selection. Opportunities for methodologic improvement in future studies of pesticides and childhood cancers are described. *Key words*: agriculture, case–control methods, childhood cancer, environment, neoplasms, occupation, pesticides, review.
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Childhood cancers are the second leading cause of death for children between 1 and 14 years of age in the United States (*1*). In recent years, the incidence of childhood cancer (specifically acute lymphoid leukemia, tumors of the central nervous system, and bone tumors) has been increasing in North America (*2*). Although relatively little is known about the etiology of childhood cancer, changes in environmental factors are potential explanations for the increase in incidence (*3–5*).

Investigations of environmental factors and childhood cancers have primarily focused on parental occupational exposures. These studies have suggested increased risks of childhood cancers in children of workers, mainly fathers, exposed to electromagnetic fields, paints, solvents, radiation, hydrocarbons, and agricultural chemicals (*6,7*). Agricultural exposures may encompass a variety of chemical and physical agents, but pesticides are usually of greatest interest. As a group, agricultural pesticides include herbicides, insecticides, fungicides, rodenticides, and other biocides. They may be found in the form of aerosols, liquids, granules, and dusts (*8,9*). Aside from occupational pesticides, no-pest strips, shampoos, and pet collars are additional forms of pesticides that may be of concern due to their use in residential settings (*9,10*). Recent studies have estimated that 78–97% of families in the midwestern United States use pesticides in or around the home (*9,11*).

The relationship between pesticide exposures and the risk of childhood cancer has been investigated in a number of epidemiologic studies; however, potential mechanisms by which pesticide exposure may lead to cancer in children remain speculative. Although carcinogenic, most pesticides are believed to be nongenotoxic. Potential genotoxic and nongenotoxic mechanisms for childhood cancer include preconceptional exposure causing mutation of parental germ cells or epigenetic effects such as alteration of imprinting patterns (*12–18*), or transplacental exposure causing somatic cell mutations in the embryo/fetus or alterations in hormonal or immunologic function (*10,19–23*). Although laboratory studies have not yet provided insight on how pesticides might act through these pathways, animal studies of other environmental agents, such as metals, alkylating agents, and radiation, have provided direct evidence for some mechanisms leading to some childhood cancers (e.g., germ cell mutation). Other carcinogenic mechanisms for environmental exposures, including pesticides, have not been thoroughly studied (*14,23–26*). Thus, linking potential mechanisms of perinatal carcinogenesis to specific exposures, including pesticides, remains a serious challenge.

Despite the limited understanding of mechanisms by which pesticides may lead to cancer, a number of associations between pesticides and childhood cancers have been reported in epidemiologic studies. The purpose of this paper is to review the methods and results of published studies of occupational and residential pesticide use and the risk of childhood cancers.

Methods and Overview

This review included published literature that assessed the risk of cancer in children associated with exposure to pesticides through parental occupation or by residential use. We included all studies identified through *Medline* published in English between 1970 and 1996. For each study, Table 1 lists the study design; time period studied with regard to pregnancy; source of cases, controls, and exposure information; and factors adjusted for in either the study's design or analysis. We used relative risk estimates when presented; otherwise we calculated odds ratios and confidence intervals from the data provided. In this paper, we will refer to relative risk estimates >1.5 as suggestive of a positive association. Risk estimates associated with occupational and residential pesticide exposure prior to conception and during pregnancy and childhood are presented in Tables 2–4 by cancer type.

Table 1 presents the key characteristics of all the studies reviewed. Because of the relative rarity of childhood cancers, most epidemiologic investigations have been case–control studies. Childhood cancer cases have been primarily identified through population-based or hospital tumor registries. Controls have been derived from a variety of sources including census records, telephone random-digit dialing, birth certificates, friends of cases, and children with other cancers or illnesses. Nearly all of the occupational studies retrospectively inferred exposure based on job title and industry rather than by direct measurement of pesticide exposure. Job title information has been obtained through interviews with parents, as well as from birth and death records. Residential exposure, which refers to pesticide use in the home and in the garden, has been assessed solely by recall of parents. Because pesticide exposure was the primary interest in only a few studies, information about both occupational and residential exposure was limited. Although some studies reported the association between pesticides and all childhood cancers combined, most studies evaluated the

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Table 1. Characteristics of studies evaluating pesticide exposure and childhood cancers

Setting and study period	Case group	Upper age bound (years)	Case (*n*)	Case source	Control source	Data source; period of interest	Design: adjusted variables[a]	Reference
Baltimore, MD, Res 1965–1975	Brain	19	84	H	BC,C	Interview; PG, CH	Age, race, sex: NA	(37)
Finland, Occ 1950–1975	Brain, leukemia	14	948	T	BC	BC; PG	Age: NA	(31)
Baltimore, MD, Occ 1965/1969–1974	Brain, leukemia	19	7,043	T,DC	BC,C	Interview; PG, CH	Age, race, sex, Dx date: NA	(30)
Los Angeles, CA, Occ 1972–1977	Brain	24	209	T	F	Interview; PG, CH	NA	(32)
Ohio, Occ 1959–1978	Brain, deaths	19	491	DC	BC	BC; PG	Age, race, sex: pat age, birth order, birth wt, percent county farmed, sex, age	(29)
Ontario, Res 1977–1983	Brain	19	74	H	PR	Interview; CH	Age, sex, region: Dx age	(35)
Ohio, Occ 1975–1982	Brain and CNS	19	110	H	RD	Interview; PC, PG, CH	Age, race, sex, region: NA	(27)
Pennsylvania, Deleware, New Jersey, Occ 1980–1986	Brain, AG	14	163	H	RD	Interview; PC, PG, CH	Age, race, region: NA	(28)
Missouri, Res 1985–1989	Brain	10	45	T	F,C	Interview; PG, CH	Age, sex: smoke, income, pat education, time from Dx to interview	(36)
United States, Canada, Res 1986–1989	Brain, AG, PNET	5	321	CCG	RD	Interview; PG,CH	Age, race, region: income	(33)
Denver, CO, Res 1976–1983	Brain, leukemia, lymphoma, sarcoma	14	252	T	RD	Interview; PG,CH	Age, sex, region: Dx age, income, mat age, mat race, mat smoke, pat education, EMF	(34)
Norway, Res[b] 1965–1991	Brain Leukemia Other	39	182 181 912	T	NA	Agricultural registry; CH	NA: age, calendar year, birth year	(38)
Finland, Occ 1973–1980	ALL	14	519	T	PR	Mail questionnaire; PG,CH	Age, sex, region: age, sex	(42)
Los Angeles, CA, Occ 1980–1984	Leukemia	10	123	T	F,RDD	Interview; PC, PG, CH	Age, race, sex, ethnicity: NA	(44)
China, Occ 1985–1986	Leukemia	14	309	T	PR	Interview; PG	Age, sex: age, sex, birth order, rural residence, mat X rays	(40)
France, Occ 1977–1982	Leukemia	NA	201	NA	I	Interview; NA	Age, sex: NA	(46)
United States, Canada, Occ 1980–1984	ANLL	17	204	CCG	RDD	Interview; PG, CH	Age, race, region: NA	(39)
Italy, Occ 1981–1984	Leukemia, lymphoma	NA	183	H	H	Interview; PG, CH	NA	(45)
Canada, Occ 1983–1985	ALL	14	128	H	PR	Interview; PG	Age, sex, region: NA	(41)
Tennessee, Res 1979–1986	ALL ANLL Other	NA	522 107 641	H	C	Interview; CH	NA: age, birth year, race, mat education, pat occupation	(43)
Texas, Occ 1964–1978	Neuroblastoma, deaths	14	157	DC	BC	BC; PG	Age: NA	(51)
Delaware, Occ 1970–1979	Neuroblastoma	NA	104	T	RD	Interview; PC, PG	Age, race, region: NA	(52)
North Carolina, Res 1967–1976	Rhabdo-myosarcoma	14	33	T	BC	Interview; CH	Age, race, sex: NA	(57)
San Francisco, CA, Occ 1978–1986	Ewing's sarcoma	31	43	T,H	RD	Interview; PC, PG, CH	Age, sex, region: income, birth year, medication, region	(48)
United States, Canada, Occ 1982–1989	Germ cell	14	105	CCG	RD	Mail questionnaire; PC, PG	NA: age, sex, live births, gestation age, mat smoke, mat education	(43)
Ohio, Occ 1950–1981	Wilms' tumor	NA	105	T	BC	BC; PG	Age, race, sex, region: NA	(50)
United States, Canada, Res 1984–1986	Wilms' tumor	15	200	CCG	RD	Mail questionnaire; CH	Age, region: income, education	(56)
Brazil, Occ 1987–1989	Wilms' tumor	NA	109	H	H	Interview; PC, PG	Age, sex, hospital, region, trimester admitted: age, sex, hospital, region, income, education	(49)
Quebec, Occ 1965–1970	Cancer, death	4	386	H	BC	BC; PG	NA	(53)

(*Table 1 continued, next page*)

Table 1. (*continued*)

Setting and study period	Case group	Upper age bound (years)	Case (*n*)	Case source	Control source	Data source; period of interest	Design: adjusted variables[a]	Reference
England, Occ[b] 1959–1963/ 1970–1972	Cancer, death	14	4,395	DC	NA	DC; CH	NA	(*54*)
Denmark, Occ 1968–1984	Cancer, general	14	1,747	T	PR	Employment registry; PC	NA// age, sex	(*55*)

All studies reviewed were case–control studies except where indicated.
Abbreviations: Res, residential; Occ, occupational; AG, astrocytic glioma; PNET, primitive neuroectodermal tumor; ANLL, acute nonlymphocytic leukemia; ALL, acute lymphocytic leukemia; H, hospitals; T, tumor registry; BC, birth certificate or registry; DC, death certificate; C, child with another cancer type; I, child with noncancer illnesses; F, friend or neighborhood; RDD, random digit dial; CCG, Children's Cancer Study Group; PR, population registry/census; PC, preconception; PG, pregnancy; CH, childhood; Dx, diagnosis; NA, information not available or not applicable to the study design; mat, maternal; pat, paternal; CNS, central nervous system; EMF, electromagnetic fields.
[a]Variables used in control selection are noted as design variables; variables controlled for in analyses are noted as adjusted variables.
[b]Study reviewed was not a case–control study.

effects of pesticides on one specific type of cancer. Because much of the research has focused on childhood brain tumors and leukemia, this review reports these studies separately from those of other cancers.

Cancers of the Brain and Central Nervous System

Both of the interview studies that evaluated paternal occupational exposure to pesticides prior to conception reported increased risks of childhood brain cancer; odds ratios (ORs) = 1.8 (*27*) and 2.7 (*28*) (Table 2). Paternal occupational exposure during pregnancy was also positively associated with childhood brain cancer risk in most studies; this was not seen for exposure during childhood (*27–31*). The results in all these occupational studies were imprecise, often dependent on a few exposed cases, and pesticide exposure was inferred by employment in agriculture and not explicitly measured. In fact, two of the five studies classified exposure based on birth certificate information (*29,31*). No studies were found that evaluated maternal occupational pesticide exposure and childhood brain cancer risk.

Childhood brain cancer risk associated with residential pesticide use varied by the type of pesticide application. Most studies found the households of brain cancer cases to be no different that those of controls in their use of professional extermination (*32–34*) or garden pesticides (*34,35*). The exception is the study of Davis et al. (*36*), which reported two- to threefold increases in risk of childhood brain cancer when pesticides were separated by type—insecticides, herbicides, or extermination of termites. Multiple studies found that parents' use of other home pesticides during pregnancy or after delivery was associated with an increased risk of brain cancer in their children (*32–34,36,37*). Both studies that evaluated exposure to no-pest strips during pregnancy or childhood reported an increased risk of brain cancer (*34,36*). Davis et al. (*36*) also reported strong relative risks associated with the use of pesticide bombs during pregnancy, childhood use of lice shampoos, and childhood contact with pesticides used on pets. This study of 45 cases was the only one to evaluate the association between residential pesticide exposure and brain cancer as the primary hypothesis (*36*). The remaining studies collected and utilized less specific information, initially evaluating residential exposure as a confounder or covariate for other primary hypotheses (*32,33,35–37*). In general, studies reporting positive effects of residential pesticide exposure were those with greater detail on the timing, frequency, and form of pesticide use (*33,34,36*).

Farm residence during pregnancy or childhood was also shown to increase risk for childhood brain cancer including primitive neuroectodermal and nonastrocytic neuroepithelial tumors, but not astrocytic gliomas (*33,37,38*). Farm residence may serve as a proxy measure for both occupational and residential pesticide exposures, but it does not indicate direct exposure to an individual. The study of farm residence by Kristensen et al. (*38*) used information on the type of crop, the amount of pesticides purchased, and the use of pesticide equipment, as recorded on 5-year agricultural census reports to classify the farm's possible pesticide exposure levels. Because the exposure information was collected for 5-year periods, this study could not isolate the time of exposure with respect to pregnancy and childhood; yet, it suggested that the risk of childhood brain cancer increased relative to the increase in the level of pesticides purchased (ORs = 2.0, 2.9, and 3.3) (*38*). Opportunities for exposure misclassification were high in these studies, but were probably nondifferential with respect to case status (*33,37,38*).

Leukemia

Although some studies classified leukemia as either acute nonlymphocytic leukemia (ANLL) (*39*) or acute lymphocytic leukemia (ALL) (*40–43*), most studies did not separately analyze these two forms of the disease. However, results from studies that made this distinction did not indicate differences in the risk of different types of leukemia associated with pesticide exposure. Because ALL is the most common form of childhood leukemia (*5*), studies that group all types of leukemias generally reflect ALL.

Five of the nine studies that evaluated occupational exposures and the risk of childhood leukemia suggested a positive association (Table 3). When studies specifically considered the use of pesticides by either parent during pregnancy rather than general employment in agriculture, the magnitude of the association with the child's risk of leukemia greatly increased (*39–41*) except in the Dutch study of ALL, which did not report positive results from a mailed questionnaire (*42*). For both parents, Buckley et al. (*39*) found an increased risk of ANLL with pesticide exposure prior to conception, as well as with prolonged pesticide exposure spanning the period 1 year before birth to diagnosis. No excess risk was found when either parent had been exposed to pesticides for less than 1,000 days; however, seven case mothers had more than 1,000 days of cumulative exposure to pesticides prior to delivery, compared to none of the control mothers ($p = 0.008$). Paternal exposure to pesticides for more than 1,000 days nearly tripled the risk of childhood ANLL (*39*). With one exception (*42*), studies of occupational exposure after the child's birth also suggested an increased risk of childhood leukemia (*30,39,44,45*).

Five studies evaluated residential exposure to pesticides. In general, no increased relative risks were associated with farm residence (*38*), garden pesticide use (*34,43*), or home extermination (*34*). However, taking into account the frequency of exposure, Lowengart et al. (*46*) reported increased risk

with frequent exposure to pesticides in either the home (OR = 3.8) or garden (OR = 6.5) during pregnancy and Buckley et al. (*39*) reported a dose–response gradient with the frequency of home pesticide exposure during childhood (ORs = 1.8, 2.0, and 3.5), although these results were imprecise. Leiss and Savitz (*34*) reported a strong association between leukemia and the use of no-pest strips in the home during either pregnancy or childhood. The two studies of leukemia that considered cumulative exposure to either occupational or household pesticides showed stronger positive associations than those classifying exposure as ever versus never (*39,46*). In general, results from leukemia studies suggest that no-pest strips and frequent use of pesticides in the home may be strongly associated with childhood leukemia (*34,39,46*), but ever using either professional exterminations or garden pesticides did not greatly impact risk (*34,43*).

Other Childhood Cancers

Among other childhood cancers (Table 4), parental occupational pesticide exposure during pregnancy was associated with an elevated risk for germ cell tumors (*47*) and Ewing's sarcoma (*48*); however, these studies were small. In a recent study of Wilms' tumor, Sharpe et al. (*49*) also reported increased risks associated with occupational pesticides, as determined through parental interview. This study also reported that the magnitude of risk for Wilms' tumor increased slightly with increased frequency of pesticide exposure during pregnancy and varied by the child's sex and age at diagnosis; male children and children who were diagnosed when they were over 2 years of age were more likely to have had either a mother or father who was occupationally exposed (*49*). This study contrasted the negative results of an earlier Wilms' tumor study that had used birth certificates to crudely determine the father's occupational pesticide exposure (*50*). Another birth certificate study reported no increased risk for neuroblastoma associated with employment in agriculture during pregnancy (*51*). A later study of neuroblastoma that used information from parental interviews supported these negative results for exposure during pregnancy, but reported increased risk for paternal employment in agriculture prior to conception, although results were imprecise (*52*). Studies that evaluated childhood cancers of all types collectively reported no increased risk with occupational pesticide exposure. These studies were limited to determining exposure status from birth certificates (*31,53*), death certificates (*54*), and employment registries (*55*). Collectively studying different cancers would not have allowed researchers to distinguish whether certain cancers had a different association with occupational pesticide exposure than others.

In a study of farm residence, Kristensen et al. (*38*) reported elevated rate ratios for Wilms' tumor, neuroblastoma, retinoblastoma, and non-Hodgkin's lymphoma in Norway; however, as previously noted, this study was unable to address the timing of exposure with regard to pregnancy or whether parents were individually exposed. Leiss and Savitz (*34*) reported no association between garden pesticide use during pregnancy and either lymphoma or soft tissue sarcoma, but soft tissue sarcoma risk was increased fourfold with garden pesticide use during childhood. Schwartzbaum et al. (*43*) also evaluated garden pesticides. This study compared the exposures of children with various types of cancer to those of children with rhabdomyosarcoma and found only the risk of osteosarcoma to be elevated with garden pesticide use. However, the use of ill children as a comparison group may be problematic (see Discussion). Finally, studies evaluating home extermination reported no increased risk for sarcomas (*34,48*), but they did report increased risk of Wilms' tumor (*56*) and lymphoma (*34*) associated with childhood exposure. Exposure during pregnancy was not associated with elevated risk of these tumors (*34,48*). It is likely that the small size of these studies of rare tumors may have contributed to their imprecise results.

Discussion

Collectively, these studies suggest an increase in risk of brain cancer, leukemia, Wilms' tumor, Ewing's sarcoma, and germ cell tumors associated with paternal occupational exposure to pesticides prior to and during pregnancy. Maternal occupational exposure during pregnancy was studied less frequently, but was also associated with leukemia, Wilms' tumor, and germ cell tumors. Most of these cancers were only evaluated in one or two studies, and the number of exposed cases was often small. Childhood brain cancer and leukemia were the most studied, with fairly consistent, moderate increases in risk (*27–31,39–42,44–46*). Farm residence was associated with brain cancers, neuroblastoma, retinoblastoma, non-Hodgkin's lymphoma, and Wilms' tumor to varying degrees. However, inference of individual-level exposure from the aggregate pesticide exposure for all farm residents limits conclusions about risk from these studies (*33,37,38*). Few studies have evaluated no-pest strips or pesticides used on pets (*34,36*); however, those studies, as well as studies of pesticide use in the home, have reported fairly consistent associations for exposure during childhood and the risk of brain cancer and leukemia, despite their small size (*32–34,36, 39,46*). It remains unclear whether a specific time window of exposure may be of greater importance in studying the effects of home pesticide use. In general, professional extermination and use of garden pesticides were less likely to show positive effects than the use of other home pesticides for most childhood cancers (*32–37,43,46,48*); however, the risk of Wilms' tumor (*56*) and lymphoma (*34*) was elevated with professional extermination use during childhood and brain cancer was elevated with termite extermination during pregnancy (*36*).

Few studies distinguished between herbicides, insecticides, fungicides, or other types of pesticides, which are not always mutually exclusive categories (*36,41*). It is possible that differences in the chemical properties of various pesticides, the methods of application, and consequently the exposure pathways (dermal, ingestion, or inhalation) may be partially responsible for the reported differences in risk of childhood cancer associated with pesticide exposure. The magnitude of the relative risks reported in these studies also appears to vary by the timing and frequency of exposure, as well as by the heterogeneity of study groups and other aspects of study design. Drawing conclusions from these studies requires careful consideration of possible methodological limitations. Exposure misclassification, insufficient sample size, biases in control selection, and uncontrolled confounding are among the primary limitations of case–control studies of pesticides and childhood cancers.

The measure of exposure in all these studies was indirect, based on parents' self-report of job titles, industry, and residential pesticide use. Information collected about home and occupational pesticide exposure has often been limited to a few general questions in an interview or questionnaire, which was rarely designed to collect detailed information about pesticide exposure. Several studies collected exposure information from birth or death certificates, which may not accurately represent the actual job, exposure, or time period of interest (*29,31,50,51, 53,54*). Thus, most studies dichotomized exposure into ever versus never exposed, without regard to the frequency or duration of exposure or the specific type of pesticide (*27–31,34–37,40–45,47,48,50–55,57*). The studies showing a positive relationship between pesticides and childhood cancers tended to be those that had *a priori* interest in pesticides and ascertained exposure in more detail with respect to timing, intensity, or pesticide type (*33,34,36,38,39,46,49,56*). By employing industrial hygienists to aid in

Table 2. Case–control studies evaluating the risk of childhood brain cancer associated with parental occupational and residential exposure and residential exposure to pesticides prior to conception, during pregnancy, and during childhood

Exposure type and frequency	Cancer type	Exposure period: Pregnancy OR	Pregnancy CI or *p*-value	Childhood Age	Childhood OR	Childhood CI or *p*-value	Reference
Occupation (Father)							
Agriculture		2.4	1.2–4.9				(29)
Agriculture		1.6	0.4–6.1	Unspec	0.9	0.3–2.9	(27)
Agriculture		2.7[a]	0.8–9.1				(27)
Agriculture		1.8[a]	0.6–6.0				(28)
Agriculture		1.0	0.2–4.3	0–1 year pre-Dx	1.3	0.7–6.3	(28)
Farmer		(1/0)[b]		Unspec	(1/0)[b]		(30)
Farmer		(1/2)[b,c]			(1/2)[b,c]		(30)
Farmer		1.2					(31)
Farm residence							
Horticulture		1.3	0.9–1.8				(38)
Pesticide		1.4	1.0–1.9				(38)
Grain farm		1.3	1.0–1.8				(38)
Horticulture	NAG	1.5	0.9–2.7				(38)
Grain farm	NAG	1.7	1.1–2.8				(38)
Pest purchase-low	NAG	2.0	0.9–4.7				(38)
Pest purchase-medium	NAG	2.9	1.5–5.6				(38)
Pest purchase-high	NAG	3.3	1.4–7.8				(38)
Farm, unspecified				Unspec	4.0	$p = 0.04$	(37)
Farm, unspecified				Unspec	1.0[c]	$p = 0.98$	(37)
Farm, unspecified	AG	0.5	0.1–1.8	Unspec	0.4	0.1–1.6	(33)
Farm > 1 year	PNET	3.7	0.8–23.9	Unspec	5.0	1.1–46.8	(33)
Garden							
Pesticide		0.6	0.3–1.1	0–2 years	0.5	0.4–0.9	(34)
Pesticide				0–2 years	0.5	0.4–0.8	(34)
Insecticide		1.5	0.6–3.9	0–6 months	2.3	0.7–8.3	(36)
Insecticide				7 months–Dx	1.6	0.7–3.6	(36)
Insecticide		1.2[c]	0.5–3.0	0–6 months	1.2[c]	0.4–3.8	(36)
Insecticide				7 months–Dx	2.6[c]	1.1–3.9	(36)
Herbicide		1.1	0.5–2.5	0–6 months	1.7	0.7–3.9	(36)
Herbicide				7 months–Dx	2.4	1.0–5.7	(36)
Herbicide		1.0[c]	0.4–2.4	0–6 months	3.4[c]	1.2–9.3	(36)
Herbicide				7 months–Dx	1.7[c]	0.7–3.9	(36)
Herbicide				Pre-Dx	0.9	0.5–1.9	(35)
Home extermination							
Ever		1.3	0.7–2.1	0–2 years	1.4	0.6–2.7	(34)
Ever				2 years–Dx	1.1	0.4–3.0	(34)
Often		1.0	$p = 0.59$	Unspec	0.9	$p = 0.29$	(32)
Ever	AG	0.7	0.4–1.4				(33)
Ever	PNET	1.0	0.6–1.9				(33)
Insects				Unspec	2.3	$p = 0.10$	(37)
Insects				Unspec	1.2[c]	$p = 0.84$	(37)
Termites, father		2.9	1.3–7.1	7 months–Dx	1.4	0.5–3.9	(36)
Chlordane, father		1.5	0.5–4.9				(36)
Pesticide (general)							
Ever		1.8	0.8–4.0	0–6 months	1.9	0.8–4.3	(36)
Ever				7 months–Dx	3.4	1.1–10.6	(36)
Ever		1.2[c]	0.5–2.9	0–6 months	1.9[c]	0.8–4.4	(36)
Ever				7 months–Dx	1.7[c]	0.5–5.4	(36)
Ever	AG	1.5	0.8–2.7				(33)
Weekly	AG	2.2	0.6–7.4				(33)
Ever	PNET	0.7	0.4–1.4				(33)
Weekly	PNET	1.0	0.2–4.9				(33)
Ever		1.5	$p = 0.08$	Unspec	1.1	$p = 0.44$	(32)
Bombs							
Ever		2.1	0.5–8.3	7 months–Dx	1.1	0.3–3.7	(36)
Ever		6.2[c]	1.4–28.4	7 months–Dx	0.6[c]	0.2–2.0	(36)
No-pest strip							
Ever		1.5	0.9–2.4	0–2 years	1.4	0.7–2.9	(34)
Ever				2 years–Dx	1.8	1.2–2.9	(34)
Ever		5.2	1.2–22.2	0–6 months	3.7	0.9–15.2	(36)
Ever				7 months–Dx	3.7	1.0–13.7	(36)
Ever		1.9[c]	0.6–5.9	0–6 months	2.5[c]	0.7–9.4	(36)
Ever				7 months–Dx	2.0[c]	0.6–6.3	(36)
On pets, insects							
Ever		0.6	0.2–1.5	0–6 months	4.8	0.9–24.7	(36)
Ever				7 months–Dx	1.4	0.6–3.1	(36)

(*Table 2 continued, next page*)

Table 2. (*continued*)

Exposure type and frequency	Cancer type	Exposure period: Pregnancy OR	Pregnancy CI or *p*-value	Childhood Age	Childhood OR	Childhood CI or *p*-value	Reference
On pets, insects (*continued*)							
Ever		0.4[c]	0.1–1.0	0–6 months	1.8[c]	1.8–6.6	(*36*)
Ever				7 months–Dx	0.7[c]	03–1.5	(*36*)
Pet collar, flea							
Ever		0.9	0.4–2.1	0–6 months	5.5	1.5–20.0	(*36*)
Ever				7 months–Dx	2.4	1.1–5.6	(*36*)
Ever		0.6[c]	0.2–1.3	0–6 months	4.4[c]	1.4–14.3	(*36*)
Ever				7 months–Dx	1.3[c]	0.6–2.9	(*36*)
Shampoo, lice (Kwell)							
Ever				7 months–Dx	1.9	0.6–6.9	(*36*)
Ever				7 months–Dx	4.6	1.0–21.3	(*36*)

Brain cancers were studied collectively unless specified. Abbreviations: AG, astrocytic glioma; NAG, non-astrocytic neuroepthelial tumor; PNET, primitive neuroectodermal tumor; Dx, diagnosis; Unspec, age of exposure during childhood was not specified in reviewed study; OR, odds ratio; CI, 95% confidence intervals.
[a]Exposure prior to conception.
[b]Unable to calculate OR; (*n* cases exposed/*n* controls exposed).
[c]Cancer control group.

the development and interpretation of structured questionnaires with job- and exposure-specific questions, the quality of information obtained from interviews may be substantially improved (*33,49,58–61*). Questions on the type of crop and purpose for pesticide use have been helpful in studies of pesticides (*58,62*). Information from new pesticide-exposure databases and reference literature can also be incorporated with the information from the questionnaires to improve exposure classification (*63,64*). In addition to improving interview questions, biological exposure data may be utilized to validate self-reported exposure information in studies evaluating recent exposures. Although the expense and logistics of collecting biological samples may be prohibitive for large-scale childhood cancer studies or studies of past exposures, smaller substudies may accommodate such direct measurement of pesticides. This information may give researchers the ability to validate and refine interview instruments to capture information on exposure routes and timing for parents and children (*61,65*).

Even when exposure assessment instruments have been used in an attempt to collect exposure information in sufficient detail, parents probably had difficulty remembering details about the frequency and timing of pesticide use relative to conception, pregnancy, and their child's diagnosis, especially when these time periods may have been up to 20 years earlier. Similarly, when both parents were not interviewed, the accuracy of the mothers' report of paternal occupational exposures is questionable (*66*). Despite investigators' efforts to elicit accurate information by parental recall, it is possible to markedly improve the quality of the information obtained. Recent studies have shown that the manner in which the question is asked (closed response options rather than open questions), the specificity of the questions, and provision of memory aids prompted improved recall (*58,59,62*). For example, Davis et al. (*36*) provided a list of pesticide brands and chemical names as a memory aid to help parents identify which pesticides were used in or around their home. In general, such aids are thought to improve exposure classification by increasing the sensitivity of reporting for both cases and controls; however, they are not thought to improve the specificity (*67*). Although many errors in exposure assessment are likely to be nondifferential with respect to disease status (*61*), differential recall based on motivation of case parents could result in an overestimate of effect, particularly in studies of childhood disease where case parents may be more motivated to find a reason for their child's illness (*68*). Highly structured interviews with detailed questions is one strategy for reducing recall bias (*60,61,67*). Unfortunately, indirect exposure assessment based on parental recall remains one of the major limitations of case–control studies, which is not easily corrected. However, until reliable and affordable biomarkers of direct pesticide exposure are developed to capture historical periods of interest, epidemiologic studies must continue to improve indirect exposure assessment tools.

Analysis of the information collected on pesticides may also be problematic. There may be multiple sources of pesticide exposure during the same time period, including home, garden, and occupational exposures by one or both parents. Most studies did not evaluate pesticides separately by specific pesticide, chemical class, frequency and duration of exposure, or account for multiple exposures; these studies also did not specify their rationale in selecting the time of interest. Limited animal data on mechanisms of perinatal carcinogenesis and consideration of human development suggests that mechanisms would differ for exposures prior to conception, *in utero*, and during childhood (*8*). By not separately considering these time windows with respect to either the timing or the cumulative effects of exposure, studies have assumed that risk is similar across all exposure windows. Despite the lack of laboratory information to guide researchers in determining which specific time periods during development are more susceptible to pesticide exposure, epidemiologic studies should consider specific exposure windows relative to conception, pregnancy, and childhood. Failure to consider interactive effects or uncontrolled confounding of pesticide exposure by multiple time periods and multiple types of exposure could bias study results in either direction (*61*).

There was also variability in case and control participation rates and study size. The participation rates in these studies ranged from 52 to 100%. Low participation rates increase the potential for selection bias, limiting the validity of study results and conclusions. These studies were generally of small sample size, forcing researchers to choose between less precise results if they attempted to control for confounding or potentially less valid results if they did not. Despite the rarity of childhood cancers, larger studies with nearly complete case ascertainment are necessary to increase the power to detect real differences between cases and controls and to allow evaluation of potential confounders and effect modifiers. In recent years, collaborative study groups including multiple children's hospitals have begun addressing this need for larger epidemiologic studies (*3,33,39,43,56*).

In principle, control selection may be the easiest methodological issue to address. Some

studies have used friends or neighborhood children for comparison. This raises concern that common parental occupational exposures, ecological exposures, and similarities in home and yard pesticide practices may overrepresent exposure in the controls and dilute potential associations. Similarly, comparison groups of children with other cancers or illnesses may attenuate effects of exposures because different childhood cancers may have some common etiologic factors. In this review, studies that compared cases to cancer controls often found no effects or inverse effects of pesticides and the cancer of interest (*30,36,37,43*). Using telephone number to randomly select controls (random digit dialing) from the same broad geographic region as the case may provide the most demographically similar control groups, without overmatching on exposures of interest (*69*).

Finally, childhood cancers are not etiologically homogeneous diseases. Studies of broadly defined disease are less likely to identify risks associated with pesticides and other risk factors when only subsets of cases are actually affected. A few studies evaluated ALL and ANLL separately, reporting little difference in their relationship with pesticide exposure (*38–42*). However, when Bunin et al. (*33*) evaluated histologic subgroups of

Table 3. Case–control studies that evaluated the risk of childhood leukemia associated with parental occupational and residential exposure to pesticides prior to conception, during pregnancy, and during childhood

		Exposure period					
		Pregnancy		Childhood			
Exposure type and frequency	Cancer type[a]	OR	CI or *p*-value	Age	OR	CI or *p*-value	Reference
Occupation, parents (either)							
Agriculture				Unspec	4.2	0.2–15.1	(*46*)
Farmer		1.3	–				(*31*)
Occupation (father)							
Agriculture		0.3	0.1–1.6				(*40*)
Agriculture		1.0	0.3–3.7				(*44*)
Agriculture		1.0[b]	0.3–1.4				(*44*)
Farmer		1.8	0.5–6.5	0–Dx	5.6	1.3–24.3	(*45*)
Farmer		(2/0)[c]		Unspec	(2/0)[c]		(*30*)
Agriculture	ALL	0.9	0.5–1.5	1 year Pre-Dx	0.9	0.5–1.5	(*42*)
Pesticide	ALL	1.0	0.6–1.7				(*42*)
Pesticide	ANLL	1.9	–	Unspec	1.8	–	(*39*)
Pesticide 1–1,000 days	ANLL	1.0	0.4–2.4				(*39*)
Pesticide >1,000 days	ANLL	2.7	1.0–7.0				(*39*)
Pesticide	ANLL	1.7[b]	–				(*39*)
Occupation (mother)							
Agriculture		2.3	0.9–6.3				(*40*)
Agriculture	ALL	1.8	0.6–5.4				(*40*)
Agriculture	ALL	1.8	0.6–6.6				(*41*)
Agriculture	ALL	0.4	0.1–1.7	1 year Pre-Dx	0.4	0.1–1.3	(*42*)
Insecticide	ALL	1.4	0.4–4.4				(*41*)
Pesticide	ALL	3.5	1.1–11.2				(*40*)
Pesticide	ALL	0.7	0.2–2.5				(*42*)
Agriculture	ANLL	1.6	0.4–6.3				(*40*)
Pesticide	ANLL	6.0	$p<0.5$	Unspec	6.0	–	(*39*)
Pesticide 1–1,000 days	ANLL	1.0	0.5–2.9				(*39*)
Pesticide >1,000 days	ANLL	(7/0)[c]					(*39*)
Pesticide	ANLL	3.0[b]	$p<0.1$				(*39*)
Farm residence	ALL	1.0	0.6–1.6				(*38*)
Garden							
Ever		1.1	0.6–1.9	0–2 years	0.9	0.5–1.18	(*34*)
>1/month		6.5	1.5–59.3				(*44*)
Ever	ALL			0–Dx	1.3[d]	$p = 0.38$	(*43*)
Ever	ANLL			0–Dx	0.9[d]	$p = 0.67$	(*43*)
Home extermination							
Ever		0.4	0.1–1.2	0–2 years	0.3	0.1–0.8	(*34*)
				2 years–Dx	0.9	0.5–1.4	(*34*)
General pesticide							
<1/week		1.4	0.8–2.2	Unspec	1.8	1.0–3.0	(*39*)
1–2/week		0.9	0.4–2.1	Unspec	2.0	0.8–5.0	(*39*)
Most days				Unspec	3.5	0.9–13.8	(*39*)
>1/week		3.8	1.4–13.0				(*44*)
No-pest strip							
Ever		3.0	1.6–5.7	0–2 years	1.7	1.2–2.4	(*34*)
				2 years–Dx	2.6	1.7–3.9	(*34*)

Abbreviations: ALL, acute lymphocytic leukemia; ANLL, acute nonlymphocytic leukemia; Dx, diagnosis; Unspec, age of exposure during childhood was not specified in reviewed study; OR, odds ratio; CI, 95% confidence interval.
[a]Types of leukemia were studied collectively unless specified.
[b]Exposure prior to conception.
[c]Unable to calculate OR; (*n* cases exposed/*n* controls exposed).
[d]Cancer control group.

Table 4. Case–control studies that evaluated the risk of other childhood cancers associated with parental occupational and residential exposure to pesticides prior to conception, during pregnancy, and during childhood

Exposure type and frequency	Cancer type	Exposure period: Pregnancy OR	Pregnancy CI or *p*-value	Childhood Age	Childhood OR	Childhood CI or *p*-value	Reference
Occupation (parents)							
Farmer	Cancer, general	1.2	$p<0.05$				(*31*)
Occupation (father)							
Farmer	Cancer, general	0.7	0.4–1.2				(*53*)
Farmer	Cancer, general	0.9	0.4–1.8				(*55*)
Farmer	Cancer, general	1.1	–				(*54*)
Agriculture	Wilms'	0.6	–				(*50*)
Pesticide	Wilms'	0.3	–				(*50*)
Pesticide <10 times	Wilms'	2.7	0.8–9.8				(*49*)
Pesticide >10 times	Wilms'	3.2	1.2–9.0				(*49*)
Pesticide	Wilms', male child	8.6	2.1–35.1				(*49*)
Pesticide	Wilms', female child	1.3	0.4–4.1				(*49*)
Agriculture	Neuroblastoma	0.6	0.2–1.4				(*51*)
Agriculture	Neuroblastoma	0.7	0.1–5.8				(*52*)
Agriculture	Neuroblastoma	3.5[a]	0.7–34.6				(*52*)
Agriculture	Ewing's sarcoma	7.3	1.9–28.4				(*48*)
Pesticide	Ewing's sarcoma	8.8	1.7–21.9				(*48*)
Pesticide	Germ Cell	1.8	0.7–5.0				(*43*)
Occupation (mother)							
Pesticide <10 times	Wilms'	0.3	0.1–2.3				(*49*)
Pesticide >10 times	Wilms'	128.6	6.4–2569.0				(*49*)
Pesticide	Wilms', male child	4.6	0.8–26.4				(*49*)
Pesticide	Wilms', female child	2.0	0.5–8.9				(*49*)
Pesticide	Germ cell	2.4	0.9–6.9				(*47*)
Farm residence							
Orchards	Cancer, general	1.9	1.2–2.9				(*38*)
Orchards	Wilms'	4.8	1.6–14.7				(*38*)
Orchard + pesticide	Wilms'	8.9	2.7–29.5				(*38*)
Pesticide	Wilms'	2.5	1.0–6.6				(*38*)
Field vegetables	Neuroblastoma	2.5	1.0–6.1				(*38*)
Field vegetables + pesticides	Retinoblastoma	3.2	0.9–10.9				(*38*)
Horticulture + pesticides	NHL	2.1	1.0–4.3				(*38*)
Pesticide	Hodgkin's	1.3	0.8–2.1				(*38*)
Pesticide	Soft tissue sarcoma	1.3	0.5–2.9				(*38*)
General	Rhabdomyosarcoma	1.0	0.2–5.2				(*57*)
Garden							
Ever	Wilms'			0–Dx	0.7[b]	$p=0.30$	(*43*)
Ever	Neuroblastoma			0–Dx	1.1[b]	$p=0.78$	(*43*)
Ever	NHL			0–Dx	1.3[b]	–	(*43*)
Ever	Hodgkin's			0–Dx	1.4[b]	–	(*43*)
Ever	Lymphoma	0.5	0.2–1.2	0–2 years	0.8	0.3–1.8	(*34*)
Ever	Lymphoma			2 years–Dx	0.6	0.4–1.0	(*34*)
Ever	Soft tissue sarcoma	0.8	0.5–1.3	0–2 years	4.1	1.0–16.0	(*34*)
Ever	Soft tissue sarcoma			2 years–Dx	3.9	1.7–9.2	(*34*)
Ever	Ewing's sarcoma			0–Dx	1.1[b]	–	(*43*)
Ever	Osteosarcoma			0–Dx	2.6[b]	$p=0.01$	(*43*)
Home extermination							
Ever	Wilms'			3 years Pre-Dx	2.4	1.1–5.1	(*56*)
>1/year	Wilms'			3 years Pre-Dx	2.2	1.3–3.8	(*56*)
>2/year	Wilms'			3 years Pre-Dx	2.2	0.9–5.1	(*56*)
Ever	Lymphoma	1.2	0.4–3.9	0–2 years	1.8	1.1–2.9	(*34*)
Ever	Lymphoma			2 years–Dx	1.6	0.9–2.9	(*34*)
Ever	Soft tissue sarcoma	0.3	0.0–1.8	0–2 years	0.5	0.1–2.4	(*34*)
Ever	Soft tissue sarcoma			2 years–Dx	0.7	0.1–5.3	(*34*)
Ever	Ewing's sarcoma	0.3	0.0–2.1	Unspec	0.6	0.3–1.2	(*48*)
General pesticide							
Ever	Rhabdomyosarcoma			Unspec	1.5	0.4–6.5	(*57*)
No-pest strip							
Ever	Lymphoma	1.4	0.7–2.5	0–2 years	1.3	0.4–2.7	(*34*)
Ever	Lymphoma			2 years–Dx	1.1	0.6–1.9	(*34*)
Ever	Sarcoma	0.6	0.1–2.6	0–2 years	0.5	0.1–2.3	(*34*)

Abbreviations: NHL, Non-Hodgkin's lymphoma; Dx, diagnosis; Unspec, age of exposure during childhood was not specified in reviewed study; OR, odds ratio; CI, 95% confidence interval.
[a]Exposure prior to conception.
[b]Cancer control group.

brain cancer, they reported different effects of pesticide exposure on astrocytic glioma and primitive neuroectodermal tumor (*33*). A study of Wilms' tumor has also suggested that risk may vary by the age of diagnosis and the sex of the child as well (*49*). In order to better understand cancer etiology, studies have recently begun to evaluate environmental risk factors for childhood cancers using cases more narrowly defined by characteristics such as histopathology, age, and biological markers (*3*).

Although many of these studies suggest an association between certain exposures and certain cancers, an etiologic relationship between pesticide exposure and childhood cancer is far from proven. Future epidemiologic research should incorporate the methodologic improvements previously noted in order to confirm and further define any association between pesticides and specific childhood cancers. Specifically, studies should carefully classify exposure with regard to chemical type and timing and more narrowly define cancer type based on histology. Laboratory investigations are also needed to provide the critical data for understanding these mechanistic relationships.

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